Critical aspects to achieve a high-quality melanoma clinic

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Critical aspects to achieve a high-quality melanoma clinic

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Purpose of review
With incidence of melanoma growing worldwide and new therapies prolonging the survival of patients with advanced disease, complex medical care is needed.

Recent findings
Best care of complicated melanoma cases is achieved in specialized referral centers. Aims to provide optimized melanoma therapy, best patient-reported treatment outcome, and successful clinical and translational research, necessitate a dedicated interdisciplinary team.

Summary
We report on critical aspects of the interaction between patients, medical care givers, clinical trial and biobanking teams, and emphasize the importance of interdisciplinary tumor boards. Specialized skin cancer nurses and local patient advocacy groups should be involved in patient care and could be the binding link between the patients and the treatment team.

Keywords
biobanking, melanoma, quality control, skin cancer center

INTRODUCTION

Even in the era of novel therapies, melanoma remains the cause of the majority of skin cancer-related deaths and hence remains the focus of experimental, preclinical, and clinical research. Accounting for less than 2% of skin cancer cases [1], it has a 5-year overall survival (OS) rate of 95–100% in stage I, 65–82.8% in stage II, 41–71% in patients with lymph-node involvement (stage III), and 9–28% in patients with distant metastases (stage IV) [2].

Melanoma has a rather heterogeneous molecular pattern of alterations, and comprises a group of malignancies, which originate from epidermal melanocytes or nevi, derived from the neural crest cells. About half harbor somatic activating mutations in the *BRAF* gene, 28% in *NRAS*, and 14% have an inactivating mutation in the *neurofibromatosis (NF)1* gene, which encodes a tumor suppressor affecting mitogen-activated protein kinase (MAPK) signaling. In cutaneous melanomas, ultraviolet (UV) signature mutations are common and are noted in 93.5% of *RAS* mutated, 92.0% of *NF1* mutated, 90.7% of *BRAF* mutated, and, interestingly, only 30% of triple wild-type melanomas. Yet, the latter group shows more complex structural arrangements and copy-number changes [3]. Cell proliferation cascade seems to have multiple interconnected points, with a good example being the co-occurrence of mutations in *NF1* and other RASopathy genes, such as *RASA2*, *SOS1*, *PTPN11*, *RAF1*, which effect RAS-MAPK signaling [4].

The origin and the pathogenesis of other less frequent melanoma types such as malignant blue nevus or spitzoid melanomas are less clear. These neoplasms have a special biology, therefore typical prognostic hallmarks such as mitotic activity, tumor thickness, and even the presence of small metastases in the locoregional lymph node should have less impact on the therapeutic strategy [5]; however, genetic markers, such as the *TERT* promoter

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KEY POINTS

- A multidisciplinary approach is needed to provide high-quality care to melanoma patients.
- A tumor board creates a space for the discussion of patient cases and for creating treatment SOPs for certain cases.
- A patient advocacy group with cancer nurse should be a part of a high-quality melanoma center.

mutations, might help to discriminate between life threatening and harmless spitzoid lesions [6].

MELANOMA THERAPY TODAY

In early stages, surgical removal of the primary tumor and in-transit or lymph node metastases is the backbone of the therapeutic strategy. Several well-designed clinical trials comparing surgical approaches such as safety margins (1–5 cm) [7–11] or lymph node dissection versus follow-up in case of microscopic involvement [12▪], have justified a patient-friendly and risk-adapted surgical management plan [7,13,14]. With the introduction of powerful systemic therapies in the adjuvant setting [15,16▪] and the development of intralesional therapies, such as talimogene laherperepvec (T-VEC) [17▪], the role of surgery might change even more in the future. The gray zone between surgery, irradiation, intralesional, and systemic therapy is critical and deserves special attention with an intensive interdisciplinary discussion.

The landscape of effective treatment options has changed dramatically over the last 6 years with the approval of nine drugs for advanced melanoma by the Food and Drug Administration (FDA) and European Medicines Agency (Fig. 1). Kinase BRAF inhibitors (BRAFi; vemurafenib and dabrafenib), MEK inhibitors (MEKi; trametinib and cobimetinib) [18,19], and immune response modulating agents [anti-CTLA-4 (ipilimumab) and anti-PD-1 antibodies (nivolumab and pembrolizumab)] [20–25] show better response rates than seen with earlier therapies, and increase the likelihood of longer survival in patients with advanced melanoma.

Recently, the only approved adjuvant therapy was interferon (IFN)-α, which showed improved relapse-free survival (RFS), but with small impact on OS [15]. Recent data of ipilimumab used in an adjuvant setting was shown to improve RFS as well as OS, when compared with placebo [16▪], and is already approved in the United States for that indication [26], whereas European approval is still pending. Adjuvant trials investigating vemurafenib, the combination of dabrafenib/trametinib, and the immune therapeutics pembrolizumab and nivolumab have been recruited, but they will need additional years before the results are available.

There is no strong consensus regarding the treatment of unresectable local disease. Radiotherapy, electrochemotherapy, isolated limb perfusion, or intralesional approaches, such as T-VEC, interleukin (IL)-2, or destructive therapies can be considered [7,14,27], whereas in unresectable metastatic disease, first-line treatment with PD-1 checkpoint inhibitor, alone or in combination with CTLA-4 inhibitor independent of *BRAF* mutation status is recommended [14].

Clinical trials with BRAFi in patients harboring *BRAF* mutations showed a clear improvement of progression-free survival (PFS) as well as OS [28–30] and were followed by trials comparing combination therapy with BRAFi and MEKi with BRAFi

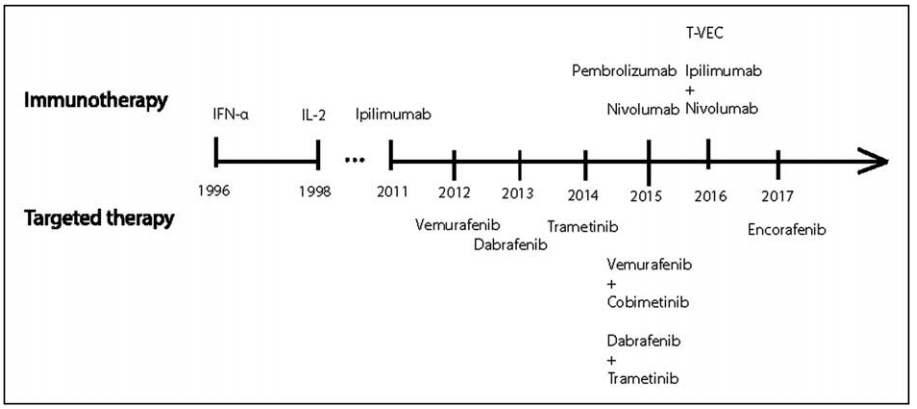

FIGURE 1. Timeline of FDA and EMA approved and pending immunotherapy and targeted therapy. BRAFi encorafenib is to be approved in 2017. EMA, European Medicines Agency; FDA, Food and Drug Administration; IFN-α, interferon-α; IL-2, interleukin-2; T-VEC, talimogene laherperepvec.

Table 1. Quality criteria for sentinel lymph node biopsy

Histology of the primary tumor should be reevaluated and provided for comparison with the sentinel lymph node (SLN)
In special forms of melanoma, such as atypical Spitz nevus, malignant blue nevus or desmoplastic melanoma, SNB has modest prognostic relevance
Re-excision with SM and SNB should be performed simultaneously, because of change in the lymph-draining (especially in head and neck)
Marking of the scar should be done during the consultation, preferably with photo-documentation
SPECT is advised in cases of unclear SLN localization
Re-excision and SNB should be performed by an experienced surgeon
Histology of SLN should be evaluated according to cell-morphology and immune-profile of the primary tumor

SM, safety margin; SNB, sentinel lymph node biopsy; SPECT, single-photon emission computed tomography.

monotherapy. Latest efficacy report from a clinical trial comparing the combination of vemurafenib and cobimetinib with vemurafenib monotherapy showed a median OS of 22.3 months [95% confidence interval (CI) 20.3–not estimable] in the first group and 17.4 months (95% CI 15.0–19.8) in the monotherapy group [hazard ratio 0.70 (95% CI 0.55–0.90), $P = 0.005$] and a 2-year OS of 48.3 and 38.0%, respectively [31▪]. Combination of new BRAFi encorafenib and MEKi binimetinib clearly showed improved median PFS of 14.9 versus 7.3 months in vemurafenib group [32▪]. Based on such results, BRAFi monotherapy is no longer advised, thus these drugs must be given in combination with MEKi whenever possible [14].

Despite these promising data, up to 50% of patients do not respond to immunotherapy [20] and about half of the patients who have achieved a clinical response (partial or complete) under a combination of kinase inhibitors eventually develop acquired drug resistance that leads to disease progression [31▪,33]. This remains an urgent unmet need for further treatment options for those patients as well as patients who harbor mutations in genes besides *BRAF* or *NRAS*.

ESSENTIAL NEEDS: INTERDISCIPLINARY TEAM AND TUMOR BOARDS IN HIGH-QUALITY MELANOMA CENTERS

In an ideal situation, the whole spectrum of medical information including cutting edge science should be considered during the process of clinical decision-making. Early stage melanomas can be treated by a single medical specialty such as dermatology or plastic surgery. However, even in these cases high-quality care in dermatology with expertise in dermoscopy of pigmented skin lesions, surgery, and high-quality dermato-pathology is mandatory.

As soon as special anatomic regions such as the head and neck are involved, several surgical subspecialists are needed to achieve an optimized surgical approach. The complexity is further increased if sentinel lymph node biopsy (SNB) is indicated. SNB results have a major impact on the patients' management; therefore, this procedure should be restricted to centers of excellence that follow high-quality standard operating procedures (SOPs) (Table 1).

The situation gets even more complex in advanced disease stages necessitating an interdisciplinary approach involving many specialties (dermatology, radiology, nuclear medicine, radio-oncology, neurosurgery, visceral surgery, plastic surgery, ear-nose-throat, pathology, psycho-oncology, etc.). Involving so many different medical specialties requires a platform wherein individual patients are discussed among all diverse specialists and a consensus decision regarding the management procedures is reached.

In our opinion the best forum for this exchange is a multidisciplinary tumor board. Patient cases, including clinical images, pathology slides and Picture Archiving and Communication System (PACS) images [computed tomography (CT) scans, PET CTs, MRIs, etc.], molecular data, and clinical features can be discussed and reviewed by the members of the board. Because not all physicians who participate in the board see the patient, it is important that the decision made by the tumor board is documented in a central electronic chart system and is automatically communicated to the major care providers of the patients outside the hospital. This ensures that the decisions of the board will be visible for everyone treating the patient in the future. As stage IV melanoma patients will be treated by different specialists and will require one treatment before another, it is also important to define the key leading physician, who will follow up on the working plan.

From our experience with tumor boards, we know that for some situations it is difficult to reach a consensus since some specialists might have different opinions regarding the treatment of a patient. This provides a unique opportunity to elaborate an evidence-based SOP for this situation so that if the next patient comes with the same problem there will

be a guideline for how to proceed. This should be elaborated outside the tumor board by a group of representatives of all specialties involved. The result of the consensus should be approved by the members of the tumor board and made available so that everyone can access them if needed. This type of meeting is called Quality Circle and should be performed at least twice a year in order to improve standardization and the quality of care for the individual patient as well as to foster the interdisciplinary exchange.

It is important to learn from unusual cases (either patients who did very well, patients with a very unusual presentation or unusual course of disease, or any other situation of special interest). The cases should be presented and discussed in detail.

Today, the pace of increasing scientific and clinical knowledge generation is dramatic. It remains an open question how innovation should be considered in the treatment decision-making. As a general worldwide principle, physician's advice about the most appropriate treatment for a given patient is well considered and based on convincing rationale, which nowadays is more and more based on the results of next-generation sequencing (NGS) and biomarkers such as programmed death-ligand-1 expression; however, this decision also reflects the physician's inclination to innovation. Although any physician may prescribe a drug, the clinical results of which are not fully known yet, thereby believing in the added value of a new treatment, others may have the more conservative tendency to rely on existing, well-established treatments. These reflections might be especially relevant for preclinical findings.

COLLABORATION WITH LOCAL PATIENT ADVOCACY GROUPS

Physicians and patients may have overlapping or divergent expectations on the outcome of cancer therapies and on the quality of medical services. However, there are hardly any communications between physicians and patients about their interaction. As a consequence, a platform for these feedback communications would be useful and advisable. An attempt to solve this problem is a regular interaction between the medical team involved and the appropriate representatives. We suggest to create a local patient advocacy group. This group is introduced to other patients who will use this opportunity to communicate about their personal experiences and to highlight positive and negative feedbacks.

IMMUNE ONCOLOGY FACULTY

Newer drugs, especially immunotherapy with checkpoint inhibiting monoclonal antibodies, can cause a wide spectrum of adverse events, most of which are immune related. These require management approaches different from those used in conventional therapy. Anti-PD-1 monotherapy is well tolerated in most cases with a frequency of grade 3/4 adverse events less than 5% for all organ systems. Anti CTLA-4 antibody ipilimumab and ipilimumab/nivolumab combinations show far more toxicity than anti-PD-1 monotherapy [34].

Fortunately, most adverse events are mild, often self-limiting or easy to treat using immune-modulating agents when identified early. However, severe adverse events can evolve into life-threatening critical situations and hence need special attention. Since more or less every organ system may be affected, there is a need for the integration of multiple disciplines in adverse event management. In our opinion, dermatology, neurology, ophthalmology, endocrinology, hepatology, and gastro-intestinology are of central relevance followed by hematology and rheumatology. In large hospitals, it is typically not realistic to inform whole teams about the specific needs during adverse event management. Therefore, it is plausible to define an individual faculty member in each department who is the principle contact person who serves for the full cancer center in his or her area of expertise.

The role of nurses during systemic therapy is particularly noteworthy. Nurses may be very well integrated in the treatment processes and be given major responsibilities, especially in keeping regular contact with patients regarding adverse events, which can occur at any time during the treatment. For many patients the inhibition threshold is lower to phone a nurse than a doctor, hence nurses could provide open and easy contact to the treatment team. It is mandatory that the nurse is familiar with the peculiar adverse event spectrum and the timing of the adverse events during the applied therapies.

BIOBANKING

The establishment of a well-managed biobank is an essential component of a highly effective melanoma clinic because it provides the basic infrastructure for conducting clinical trials and is the foundation of a cutting-edge translational oncology research programme. However, in order to ensure reproducibility and the most effective use of biological samples, biobank teams must be cross-trained in all preservation techniques, and clear SOPs need to be strictly implemented, maintained, and updated.

The choice of what samples to collect and how to preserve them depends largely on local ethical review boards, patient consent, the kinds of clinical trials being run, and the available resources for treating and storing samples. A thorough biobanking programme will include blood samples and tumor biopsies, but how these are further processed depends largely on the intended downstream applications. Obviously, there should be a strong preference for preservation techniques that allow for diverse experiments subsequent to storage. Historically, tumor material has been kept mostly in formalin fixed paraffin embedding (FFPE), and although DNA and RNA extraction techniques have recently improved from FFPE tissues, many experiments such as fluorescence-activated cell sorting or cell line culturing are no longer efficient or possible once a tumor has been preserved in FFPE.

A melanoma biobank that includes FFPE samples but that also cultures live cells from surplus material [35] can provide an excellent resource for subsequent mechanistic studies. Here it is also critical that there is effective communication between clinical and translational research teams to make the best use of the material. For instance, attending physicians may know important details about individual patient progression patterns that are directly relevant for subsequent scientific studies. Not only does such knowledge help scientists choose the best samples for their experiments, but it also helps focus translational research projects on the most clinically relevant problems.

The advent of NGS technologies and increasingly more specific molecular pathway inhibitors promise a new era of precision medicine with individualized therapies that are more effective than previous broad-spectrum approaches to fighting cancer. However, the high-dimensional datasets produced by whole-exome or whole-genome sequencing as well as RNA sequencing or even proteomic approaches [36,37] introduce a new set of problems for clinicians. Molecular tumor boards are intended to solve that problem by reducing high-dimensional datasets (for instance from whole-exome sequencing) to an actionable list of targets and approved drugs that may be readily available for therapeutic interventions.

Although it is clear that molecular tumor boards should be implemented to provide clinical decision support, there are still few examples of effective use of NGS data in routine clinical practice. Whereas the integration of these datasets in a tumor board setting is necessary in the future, a great deal of work needs to be done to first, collect data from multiple omics platforms (e.g., gene expression, copy-number alterations, single nucleotide polymorphisms, mutation burden, HLA-type, T-cell receptor repertoire, proteomics, etc.); second, define standard, robust bioinformatics pipelines with documentation; third, curate databases of drug–gene interactions for clinical practice; and finally, reduce the relevant data into simple but accurate reports for a clinical audience.

As our understanding of molecular pathways improves along with our ability to target them, molecular tumor boards will become even more useful and ubiquitous. Because of the complex and evolving nature of the task, interdisciplinary teams of experts must meet regularly to develop protocols and optimize them to provide the best possible care to melanoma patients according to the latest scientific developments.

CONCLUSION

Modern melanoma management is a paradigm for precision medicine in a rapidly evolving scientific environment. Networking and cooperative projects with basic research on a local, national, and international level are crucial. It is especially attractive to include well-established local basic research groups and search for cooperative projects including the investigation of patient samples collected in the biobank. Clinical research with pharma-sponsored and investigator-initiated clinical trials is necessary to create a critical understanding of clinical science. Patients should be regularly informed about these projects and may even actively support these efforts.

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Conflicts of interest

There are no conflicts of interest.

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